I. REMARKS

Claims 128-131, 135-137, and 146-148 are pending in this application. Claim 150 is canceled and new Claims 151-157 are added herein. New Claims 151-157 are supported by the specification and claims as originally filed. A Petition for Extension of Time along with the requisite fee accompanies this Response. BattellePharma, Inc. has changed its name to Ventaira Pharmaceuticals, Inc. Information about Ventaira may be found at our website at www.ventaira.com.

II. Rejection Under 35 U.S.C. §112, 2nd Paragraph

Claim 130 is amended herein to depend from Claim 129 which provides antecedent support for the term "said anthracycline" in claim 130. Claim 137 is amended herein to delete the word "anthracycline". It is believed that these amendments obviate Examiner's rejection of Claim 130 and 137 under Section 112, 2nd paragraph.

III. Rejection Under 35 U.S.C. §102(e)

Claims 128-130, 135, 136, and 150 are rejected under 35 U.S.C. 102(e) as being anticipated by Kaufman et al. (US 5,770,585). Examiner contends that Kaufman discloses the following:

> "... a method of treating lung cancer (respiratory cancer) comprising delivering a liquid dispersion (aerosol liquid) or breathable gas (inhalation) containing an anthracyline such as doxorubicin to the lungs."

Kaufman describes liquid dispersions consisting of a perfluorocarbon liquid, water, surfactant and active drug substance. These liquid dispersions are administered intratracheally into the lungs. The reference at Col. 8, lines 1-67 and Col 9, lines 4 provides a detailed description of how the dispersions are administered. Contrary to Examiner's assertion, Kaufman does not teach that his liquid dispersions are aerosols or that they may be delivered or administered as an aerosol via inhalation.

Liquid perfluorocarbons (PFCs) are biochemically inert with high gas solubility properties. Perflubron [perfluorococtyle bromide] (PFOB) is in clinical development for use in partial liquid ventilation to improve oxygenation and pulmonary function. Kaufman prepares liquid dispersions containing perfluorocarbons such a PFOB and uses these dispersions to deliver an active drug to the lung.

Certain perfluorocarbons are "breathable liquids" because of the high solubility of oxygen in the perfluorocarbon liquid. In 1966, Clark and Gollan, [*Science*, **152**, 1755-1756 (1966)] demonstrated the ability to provide adequate gas exchange during spontaneous liquid breathing of perfluorocarbon by the mouse. In these experiments, mice were totally immersed in a liquid perfluorocarbon that was saturated with oxygen and they were able to "breathe".

Since the early experiments with mice, PFCs such as perflubron have been extensively studied in humans for their ability to enhance gas exchange and pulmonary function in the setting of lung injury. Liquid ventilation with PFC has been performed in general, by one of two techniques: (1) total liquid ventilation, in which the lungs are filled with PFC and ventilated with tidal volumes of PFC using a liquid ventilator; and (2) partial liquid ventilation (PLV), in which the lungs are filled with PFC and then ventilated with gas tidal volumes using a standard gas ventilator. U.S. Pat. 5,158,536 (Sekins et al.) cited in the Kaufman reference contains a lengthy list of journal articles relating to the use of PFCs as blood substitutes as well as the use of PFCs in liquid ventilation.

Kaufman does not deliver drug to the lungs of a patient via administration of an aerosol. The reference describes the instillation of a liquid directly into the lungs. This might be done as a lavage (Col. 4, line 51)), intratracheally, i.e. via a tube, or as part of a liquid ventilation procedure (Col.4, line 26). The liquid dispersion is not aerosolized prior to administration and it is not delivered using an inhaler or nebulizer. Kaufman teaches that intratracheal administration of the liquid dispersions of his invention is superior to the prior art method of delivering such drugs via metered dose inhalers (Col. 4, lines 48-52).

Kaufman teaches (Col. 2, lines 62-67 and Col. 3, lines 9) that the liquid dispersions of his inventions as well as the method of delivering a drug in such liquid dispersions has several benefits and advantages, one of the primary advantages being,

> "... the ability to incorporate and deliver a drug to the lung of an animal in a formulation which provides sufficient gas exchange during liquid ventilations."; and
>
> "... delivery of .. therapeutic agents by this method is an enormous improvement over current techniques, since the active agent is uniformly distributed across the entirety of the alveolar space, making it available to the distant small alveolar beds which are not accessible by nebulization or aerosolization technologies."

Kaufman clearly teaches one skilled in this art that the instillation method of his invention is different from and in Kaufman's opinion superior to, pulmonary administration of an aerosolized liquid medicament to the lungs of a patient.

In order to "anticipate" the invention claimed herein, the Kaufman reference must disclose each and every element of the claimed invention arranged as in Applicants claims. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.,* 221 USPQ 481. Kaufman teaches that the WIP dispersions of his invention should be delivered to a patient by instillation (intratracheally) or by liquid lavage. Applicants claimed method requires delivery (administration) of an aerosol via inhalation. Kaufman specifically teaches that delivery of an aerosol is undesirable. It is respectfully asserted that the Kaufman reference does not anticipate Applicants" claimed invention because it does not disclose each and every element of Applicants claimed method.

IV. Rejection Under 35 U.S.C. §103(a)

Applicants' invention is to a method of administering a vesicant anticancer agent to the lungs of a patient by pulmonary delivery of an aerosol of the drug. The patient breathes in the aerosol which can be formed using conventional aerosolization means such as a nebulizer of the type disclosed in US Pat. 6,269,810 or an electrohydrodynamic aerosolization device such as that disclosed in US Pat. 6,397,838.

In contrast, the invention of Kaufman is directed to homogeneous water in perfluorocarbon ("WIP") dispersions containing a drug where the drug is dissolved in the aqueous phase liquid if it is hydrophilic and in the continuous liquid perfluorocarbon phase if it is lipophilic. Contrary to the Examiner's characterization of what Kaufman teaches, the WIP dispersions of Kaufman are neither an aerosol nor are they administered by the patient's inhalation of an aerosol. The WIP dispersions of Kaufman are liquids which are administered to the patient by instillation; i.e., a tube is passed through the trachea into the lungs and the liquid is placed into the lungs (See Col.8, lines 28-67 and Col. 9, lines 1-4). In fact, Kaufman teaches the superiority of drug delivery using the liquid WIP dispersions of his invention over delivery via nebulization or aerosol techniques. See Col. 3, lines 1-6 and Col. 4, lines 48-52.

When the WIP dispersion of Kaufman is instilled into the lung, the active drug substance does not directly contact the lung surface since it is either in solution, in a micelle or a liposome. One of the surprising features of Applicants' invention is that it is possible to deliver therapeutic amounts of a "vesicant" anticancer drug to the deep lungs of a patient without causing necrosis, or tissue damage to the surface of the alveoli.

The Kaufman reference contains no teaching or direction regarding the issues associated with administering vesicant drugs to a patient via IV much less via inhalation of an aerosol. The active drug substance in the dispersions of Kaufman are either in solution, or in micelles or liposomes when such dispersions are instilled into the lungs. The tissue of the lung is not directly exposed to the active drug substance in Kaufman's WIP dispersions.

One skilled in the art of clinical oncology is very familiar with the sometimes devastating damage caused when a vesicant anticancer agent is extravasated during IV administration. At the time Applicants invention was made, it was very surprising that vesicant anticancer drugs could be administered via inhalation of an aerosol without causing damage to the mouth, throat and lungs. Attached (Tab I) is a copy of the Rule 132 Declaration of Dr. Stephen K. Carter filed in USSN 09/000,775 now US Pat 6,471,943 , the parent of this application. As indicted by Dr. Carter's *curriculum vitae*, he is an expert in the area of clinical oncology research.

As pointed out by Dr. Carter, it is well known in the art that vesicant anti-cancer agents such as anthracyclines, taxanes, vinca alkaloids and alkylating agents can cause injury and even tissue death when tissue is exposed to these vesicating drugs. (See p. 2, para.2 and p. 3, para. 1 of the Declaration).

In his Declaration Dr. Carter stated:

> "...it was totally surprising to me...that doxorubicin was being administered directly by inhalation...it is widely known in the field of oncology that doxorubicin is a highly toxic vesicant which kills living tissue on contact."

Dr. Carter goes on to discuss the problem of extravasation of a highly vesicating drug and states that:

> "Extravasation occurs when a highly vesicating drug, such as doxorubicin, is being given intravenously (IV) and some of the drug inadvertently, whether by improper administration or leakage of the blood vessels, leaks into the tissue surrounding the vein...[I]t has been reported ... that patients have lost limbs when doxorubicin was extravated into surrounding tissue."

Dr. Anthony R. Imondi a co-inventor of the subject matter claimed herein, has over 35-years of experience in cancer research. The Rule 132 Declaration (copy attached as Tab II) submitted by Dr. Imondi during prosecution of the parent application USSN 09/000,775, supports the following important points:

- When animal studies were begun to study the effects of inhaled doxorubicin it was unknown if even small doses of inhaled doxorubicin could be tolerated, or even if any of the drug could be tolerated in the lungs.

- Based on his knowledge of the necrotizing effects of doxorubicin and its vesicant properties, it was unexpected that doxorubicin could be administered by inhalation at doses sufficient to inhibit or shrink tumors in the lung without causing intolerable toxicity.

- The Food and Drug Administration (FDA) well aware of the vesicant properties of doxorubicin required Applicants to perform toxicology studies in dogs that exposed the entire mouth of the dog to aerosolized doxorubicin and to do complete microscopic examination on the structures of the dog's mouths before allowing the treatment (method of the invention) to be given to human patients with cancer.

- Surprisingly, the dog studies failed to show any toxicity to the mouth.

It is respectfully asserted that Kaufman fails to teach or suggest the method claimed herein and in fact, that Kaufman actually teaches away from Applicants' claimed invention because he suggests that administration of an aerosol containing the drug to the lungs is inferior to the method disclosed by Kaufman. Further, as evidenced by the Rule 132 Declarations filed by experts in the art of clinical oncology, it was very surprising that one could administer a vesicant anticancer drug directly to the lungs of a patient without causing damage to the mouth, throat and lungs.

V. Double Patenting Rejection

Applicants respectfully contend that there is no issue of "double patenting" presented in connection with this application USSN 10/066,831 and the other members of its family. As summarized in the following Table 1 and Table 2, this application, as well as four (4) other applications are all continuations of USSN 09/000,775.

Table 1
Family History of USSN 10/066,831

Case No.	Serial No.	Filing Date	Issue Date	Expiration Date	Patent No.
0	60/033,789 Provisional	12/30/1996	----	Expired	
1	09/000,775	12/30/1997	10/29/2002	12/30/2017	6471943
2	09/517,915	03/30/2000	09/17/2002	12/30/2017	6451784
3	09/875,680	06/06/2001	02/19/2002	12/30/2017	6348209
4	09/875,345	06/06/2001	04/16/2002	12/30/2017	6419900
5	09/875,677	06/06/2001	07/16/2002	12/30/2017	6419901
6	10/066,831	02/04/2002			

Table 2

Summary of Patent/Claim Status

Serial No.	Patent No.	Family Status	Independent Claim
09/000,775	6471943	Application claims the benefit of U.S. Provisional Application No. 60/033,789 filed on Dec. 30, 1996.	1. A method for treating a patient having a neoplasm comprising: administering a pharmaceutically safe and effective amount of non-encapsulated doxorubicin to said patient by inhalation, wherein said safe and effective amount provides an animal dose of about 2 to 90 mg/m^2 or a human dose of about 3 to 130 mg/m^2, wherein both doses are based on body surface area, and wherein said doxorubicin is inhaled in an aerosol.
09/517,915	6451784	Application is a con't of USSN 09/000,775, filed Dec. 30, 1997, which claims the benefit of U.S. Provisional Application No. 60/033,789 filed on Dec. 30, 1996.	1. A method of treating cancer of the respiratory tract in a patient which comprises administering to said patient a pharmaceutically safe and effective amount of an aerosolized anticancer agent consisting essentially of carboplatin, wherein said carboplatin is administered at a dosage of from about 0.24 mg/m^2 body surface area to about 16.0 mg/m^2 body surface area; and wherein said carboplatin is delivered to said patient using a means for aerosolization of said carboplatin.
09/879,677	6419901	Application is a continuation of 09/000,775 filed Dec. 30, 1997 which claims the benefit of U.S. Provisional Application No. 60/033,789 filed on Dec. 30, 1996.	1. A method of treating cancer of the respiratory tract in a patient in need of treatment which comprises administering by inhalation a pharmaceutically safe and effective amount of a vesicant anthracycline anti-cancer agent, wherein said anti-cancer agent is unencapsulated.
09/875,345	6419900	Application is a continuation of 09/000,775 filed Dec. 30, 1997 which claims the benefit of U.S. Provisional Application No. 60/033,789 filed on Dec. 30, 1996.	1. A method of treating cancer of the respiratory tract in a patient in need of treatment which comprises administering by inhalation a pharmaceutically safe and effective amount of a vesicant taxane anti-cancer agent, wherein said anti-cancer agent is encapsulated.
09/875,680	6348209	Application claims the benefit of U.S. Provisional Application No. 60/033,789 filed on Dec. 30, 1996, and is a continuation of Ser. No. 09/000,775 filed on Dec. 30, 1997.	1. A method of treating cancer of the respiratory tract in a patient in need of treatment which comprises administering by inhalation a pharmaceutically safe and effective amount of a vesicant vinca alkaloid anti-cancer agent; wherein said anti-cancer agent is unencapsulated.

A comparison of independent Claim 1 from each of the issued patents indicates that the claim scope is different in each patent and from the claim scope set forth herein.

All of the applications and patents listed in Table 1 and Table 2 were filed after the parent application USSN 09/000,775 and before USSN 09/000,775 issued as US Pat. 6,471,943. All of the patents listed in Table 2 belong to BattellePharma (now Ventaira, Pharmaceuticals, Inc.); thus, they are under common ownership.

All of the patent applications and resulting patents relating to this application are owned by the same entity. All of the applications, including this application were filed after the parent application USSN 09/000,775 and before the "775 application issued as a patent.

It is Applicants understanding that the term of all of the patents issuing from the continuation applications (including this one) will expire on the same day as the parent US Pat. 6,471,943; i.e., December 30, 2017.

Applicants respectfully assert that the double patenting issue raised by Examiner has been obviated by the explanation presented herein and that this rejection will be withdrawn.

Conclusion

Based on the amendments and arguments presented herein, it is asserted that all of Examiner's objections and rejections have been overcome and that this application is in condition for allowance. Examiner is respectfully requested to withdraw all rejections and to issue a Notice of Allowance.

Respectfully submitted,

Dated: January 28, 2004

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